PATENT

UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	STEVENS, Fred J. et. al.
Title:	FIBRIL-BLOCKING PEPTIDE, A METHOD FOR PREVENTING FIBRIL FORMATION
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AMENDMENT TO SPECIFICATION

Sir:

In response to the July 2, Notice to Comply with the Sequence Rules in the above-identified matter, applicant requests entry of the changes to the specification page 15, as marked on the following sheet.

FIG. 4 depicts the inventor's competitive inhibition model. SMA fails to progress along a productive folding pathway and hence both of its domains remain in the reduced state *in vivo*. The presence of the highly unstable κ4 protein is detected by BiP, presumably during or soon after its translocation across the ER membrane. Binding to BiP prevents SMA aggregation in the lumen and facilitates its dislocation back to the cytosol. Once there, binding to Hsp70 (or related chaperones) serves to maintain SMA in a degradation-competent state, so that it can be ubiquitinated and rapidly targeted to proteasomes. At the same time, Hsp70 inhibits the tendency of SMA to aggregate in the cytosol, thus regulating the balance between degradation and aggregation.

The inability to fold exposes (at least) the two major peptides in each of the two β sheets of the V domain that are good sites for binding of Hsp70 family chaperones. Continued exposure of these sites enables associations first with BiP (within the ER) and then with Hsp70 (in the cytosol). The FTLTISS --(SEQ. ID. NO. 1)-- peptide which is effective in reducing intracellular aggregation has the sequence of one of these two major sites, and importantly, the same features that are required for its anti-aggregation activity are necessary for its Hsp70 binding activity.

The inventors envisage the peptide to interact with the same amino acids in the hydrophobic core of the V domain normally occupied in the folded molecule by the endogenous FTLTISS --(SEQ. ID. NO. 1)-- peptide. In this way, the peptide acts as a surrogate chaperone, inhibiting aggregation and promoting degradation. This provides a new avenue for treatment modalities using rationally designed peptides to suppress aggregation.

While the invention has been described through the embodiments disclosed herein, it should be noted that the embodiments are not intended to limit the scope of the following claims.